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(54) Title: 5-HT ₂ RECEPTOR ANTAGONIST COMPOSITIONS USEFUL IN TREATING VENOUS CONDITIONS (57) Abstract Treatment of compositions containing 5-HT ₂ receptor antagonists useful in treating such venous conditions as hemorrhoids, varicose veins, venous insufficiency and wounds. In particular it comprises use of a 5-hydroxytryptamine-2 receptor antagonist (5-HT ₂) at an effective therapeutic dose to treat a human or animal suffering from such a condition. The 5-HT ₂ receptor antagonist can also be administered prophylactically.		

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5-HT₂ RECEPTOR ANTAGONIST COMPOSITIONS USEFUL IN
TREATING VENOUS CONDITIONS

This invention relates to the treatment of and to compositions containing 5-HT₂ receptor antagonists useful in treating such venous conditions as hemorrhoids, varicose veins, venous insufficiency and wounds. In particular it comprises use of a 5-hydroxytryptamine-2 receptor antagonist (5-HT₂) at an effective therapeutic dose to treat a human or animal suffering from such a condition. The 5-HT₂ receptor antagonist can also be administered prophylactically.

Serotonin or 5-hydroxytryptamine or 5-HT is a vasoconstrictor and a powerful stimulant of a variety of smooth muscles and nerves. A derivative of the amino acid tryptophan, 5-HT is formed predominantly in enterochromaffin or argentaffin cells of the intestinal tract. It is transported in the blood by platelets and is present in the brain and other tissues. Its pharmacological actions result in a variety of responses involving, inter alia, the cardiovascular, respiratory, and gastrointestinal systems, smooth muscles, exocrine glands, carbohydrate metabolism, sensory nerve endings, autonomic ganglia, the

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adrenal medulla, and the central nervous system.

Cellular reaction is determined by the type and number of receptors on the outer membrane of the cells. Consequently, one hormone can trigger different responses in different cells because it may have different receptors. Thus, the same hormone that can contract one smooth muscle cell, can also relax a skeletal muscle cell having a different receptor to the same hormone. This is true for 5-HT.

There are many receptors for 5-HT that control the various cellular responses which are mentioned above. To identify the different receptors to a specific hormone (e.g. 5-HT), several methods are used. For example, in labeling studies, the labeled hormone binds to a specific receptor. The antagonists are classified according to their ability to displace the labeled hormone from the receptor in question. Those that can displace it from a particular receptor are said to be antagonists to that receptor. Some antagonists can displace the hormone from one receptor without affecting its binding to another, and the degree of selectivity can thus be determined. In pharmacological studies, the ability of antagonists to antagonize some of the effects of the hormone thought to be related to one receptor or another are examined. A suitable example relates to the hormone histamine. Some antagonists (histamine-2 antagonists) can antagonize its acid secretory receptors with little or no effect on its lung receptors and thus inhibit acid secretion by the stomach without causing bronchodilatation. Other antagonists (histamine-1 antagonists) antagonize

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histamine's lung effects with almost no activity against its acid secretory effects. Biochemical studies are those in which the biochemical effects of the hormone in question can be
5 antagonized selectively by one receptor antagonist or another.

Serotonin receptors are divided into several classes, one of which is referred to as the 5-HT₂ receptor. A complete discussion of
10 such receptors will be found in "The Peripheral Actions of 5-Hydroxytryptamine" edited by John R. Fozard (Oxford University Press, 1989). Receptors for 5-HT have been classified based on the responses they produce when stimulated by 5-
15 HT. At present four main classes and several subclasses of 5-HT receptors are generally recognized. The four main classes are:

5-HT₁ receptors: These receptors appear to mediate the relaxation of smooth
20 muscles and increased heart rate.

5-HT₂ receptors: These receptors appear to mediate vasoconstriction and platelet aggregation.

5-HT₃ receptors: These receptors
25 appear to mediate vomiting by action in the central nervous system.

5-HT₄ receptors: These receptors mediate effects not covered by the other three receptors.
30 (P.A. van Zwieten et al. "Pathophysiological and Pharmacotherapeutic Aspects of Serotonin and Serotonergic Drugs," Clin. Physiol. Biochem. 8 (suppl 3), 1 - 18, 1990 Frazer et al. "Subtypes of Receptors for Serotonin" Ann. Rev. Pharmacol
35 Toxicol. 30, 307 - 348, 1990)).

The Frazer article shows that serotonin has different receptors sometimes

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mediating opposite effects. Thus a multitude of different and sometimes opposite effects can be induced by 5-HT receptor antagonists. 5-HT receptor antagonists produce different pharmacological responses depending on the type and location of the 5-HT receptor they antagonize or block. They produce a variety of different responses in the central nervous system. Peripherally, such antagonists can sometimes produce antagonistic responses. This is similar in many respects to the Histamine antagonists. Histamine-1 (H-1) antagonists inhibit bronchioconstriction but have no effect on gastric acid secretion while Histamine-2 (H-2) antagonists inhibit gastric acid secretion with no effects on the lungs. Thus a general statement that histamine antagonists should be good for acid secretion or bronchio-spasm is meaningless.

5-Hydroxytryptamine (5-HT₂) receptor antagonists are different from other 5-HT receptor antagonists in many respects in that 5-HT₂ receptor antagonists:

a. Antagonize serotonin stimulation of intra-cellular calcium levels via stimulation of phosphoinositide hydrolysis in smooth muscle, human and rabbit platelets and astrocytes.

b. Antagonize serotonin contraction of the canine and human basilar artery while producing no hypotension.

c. Antagonize the increased vascular permeability induced by 5-hydroxytryptamine

d. Antagonize the head shakes and twitches in rodents induced by serotonin.

5-HT can induce both contraction and relaxation in blood vessels. The type of responses produced depends on the type of

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receptor present. For example, 5-HT₂ receptor stimulation contracted the porcine coronary arteries (Daniel J. Cushing and Marlene L. Cohen, "Comparison of the Serotonin Receptors That Mediate Smooth Muscle Contraction in Canine and Porcine Coronary Artery" J. Pharmacol. Exptl. Therapy. 261, 856 - 862, 1992) but dilated the canine renal artery (Shoji et al. "Renal Vasodilation Induced by DOL, a 5-HT₂ Receptor Agonist, in the Canine Kidney" Europ. J. Pharmacol. 190, 247 - 250, 1990) Stimulation of 5-HT- receptors produced constriction in the canine Savenous vein (Else Muller-Schweinitzer, "Venoconstrictor Responses to Dihydroergocristine and Dihydroergotamine: Evidence for the Involvement of 5-HT₁ Like Receptors" Cardiovascular Drugs and Therapy, 4, 1455 - 1460, 1990), the rabbit saphenous vein, (Dicky Van Heuven - Nolsen et al. "5-HT₁ Like Receptors Mediate Contraction of the Rabbit Saphenous Vein" Europ. J. Pharmacol. 191, 375 - 382, 1990) but dilated the small arteriols in rat skeletal muscles (Nancy L. Alsip et al. "Multiple Serotonin Receptors on Large Arteriols in Striated Muscle" Blood Vessels, 28, 537 - 541, 1991). These are only example. For more examples see (Sahin-Erdemli et al. "5-HT₁ like Receptors Mediate 5-hydroxytryptamine-induced Contraction of Guinea-pig Isolated Iliac Artery" Brit. J. Pharmacol., 102, 386 - 390, 1991; Fong M. Lai et al. "Characterization of Serotonin Receptors in Isolated Rat Intramyocardial Coronary Artery" J. Pharmacol., Exptl. Therapy., 256, 164 - 168, 1991; Hubert Dabire et al., "Hemodynamic Aspects and Serotonin," Clin. Physiol. Biochem. 8 (suppl 3), 56 - 63, 1990; M.J. Summer, "Characterization of the 5-HT

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receptor Mediating Endothelium-Dependent Relaxation in Porcine Vena Cava," Brit., J. Pharmacol., 102, 938 - 942, 1991; B.N.C. Prichard and C.C.T. Smith, "Serotonin: Receptors and Antagonists - Summary of Symposium," Clin. Physiol. Biochem. 8 (suppl 3), 120 - 128, 1990, Lubo Zhang and Donald C. Dyer, "Characterization of Serotonergic Receptors Mediating Contraction of Ovine Umbilical Artery" J. Pharmacol., Exptl. Therapy. 255, 233 - 239, 1990).

In fact 5-HT can mediate both contraction and relaxation in the same tissue (Zeljko S. Radic et al., "Alterations in Serotonergic Receptor Expression in Experimental Vein Grafts;" J. Vascular Surgery 14, 40 - 47, 1991).

Tissues respond to hormones only if they possess specific receptors capable of recognizing and interacting with the hormone in question. The selective and sometimes opposite responses of different tissues to the same hormone, in this case 5-hydroxytryptamine (5-HT) or serotonin, is determined by the type and density of the receptors to the hormone that exist in the particular tissue. It is not possible to predict the activity of 5-HT receptor antagonists in a particular disease condition unless the tissue involved in that disease is tested. For example, 5-HT will not contract the colon vein of cats or dogs since the colon veins from both animals species have no 5-HT receptors. 5-HT will contract the human colon vein because the human colon vein contains 5-HT₂ receptors that mediate contraction. (see example below). In the human colon, 5-HT₂ receptor antagonists are expected to antagonize the increased contraction of the colonic veins

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induced by 5-HT (shown in the data) and decrease the vascular permeability that mediate the swelling and discomfort of hemorrhoids. Other 5-HT receptor antagonists (as 5-HT₁ 1A, 1B, 1C, 1D, 1P and 3) will not mediate these effects and are expected to have no beneficial effects in treating hemorrhoids, varicose veins, venous insufficiency and the healing of wounds.

In the past, before the inventor's present understanding of the different receptors and actions of 5-HT was discovered, it was customary to regard all 5-HT receptor antagonists as constituting one category and to assign common actions to all of them. This was what was done in South African Patent 85/2785 (Merck & Co). This reference as well as U.S. Patent 4,665,075 (Vandenberg), European Patent 0037265 (Kennis), South African Patent 854161 (Merck) and U.S. Patent 4,539,318 (Baldwin) suggest, without support, a connection between anti-serotonin activity and anti-hemorrhoidal effects. None of these references show any applicable data. Patents published in the 1980's generally assumed that anti-serotonin activity should translate into anti-hemorrhoidal effects since the hemodynamic effects should, on theoretical grounds, be helpful. In addition, most anti-hypertensive drugs were thought to possess anti-hemorrhoidal activity. This has no basis in fact.

Specific 5-HT₂ receptor antagonists produce several effects including inhibition of platelet aggregation and decreasing vascular permeability. 5-HT₂ receptor antagonist compounds have traditionally been used as anti-anxiety agents, antidepressants, antipsychotics, anti-migraine agents or as modifiers of certain

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other CNS functions. 5-HT₂ receptor antagonists, do not cause vasodilation in the arteries and do not lower blood pressure. This is shown in the example below where the 5-HT₂ receptor antagonist 2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride do not lower blood pressure. This is also exemplified by ritanserine and ICI 169, 269 (Gerard J. Blauw et al., "Antihypertensive Treatment with Ketanserine Shows No Evidence of Vascular Serotonin - Receptor and alpha-Adrenoceptor Blockade" Drugs, 40 (suppl 4), 42 - 44 1990; P.A. van Zwieten et al. "The role of 5 hydroxytryptamine and 5-hydroxytryptaminergic Mechanisms in Hypertension, "Brit J. Clin. Pharmacol., 30, 695 - 745, 1990: Bengt Persson, et al., "Antihypertensive Effects of Ketanserine and Ritanserine in the Spontaneously Hypertensive Rat," J. Cardiovasc. Pharmacol., 11 (suppl. 1. 522 - 524, 1988). The compounds disclosed in South African patent 85/2785 all lower blood pressure indicating that they could not be selective 5-HT₂ receptor antagonists.

Serotonin is not a general endogenous vasoconstrictor. Its effects in the different blood vessels varies depending on the location and size of the vessel in question (P.A. van Zwieten et al., "Pharmacological Profile of Antihypertensive" Drugs with Serotonin Receptor and alpha-Adrenoreceptor Activity Drugs 40 (suppl 4) 1 - 8, 1990). Hemorrhoids is a disease of veins not arteries. Drugs that are expected to have beneficial activity in hemorrhoids must be able to antagonize the contractile effects of 5-HT on the colon vein. Hemorrhoids is a varicose dilation of veins in the superior or inferior hemorrhoidal plexus,

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resulting from a persistent increase in venous pressure" (Dorland's Illustrated Medical Dictionary, 25th Edition, W.B. Saunders, Philadelphia, 1974).

5 Hemorrhoids refer to a madd of dilated veins in swollen tissue situated near the anal sphincter. They are believed to result from a persistent increase in venous pressure, which may be due, in part, to a constriction of the
10 large downstream colonic veins. Occlusion due to platelet aggregation and thrombus formation may also contribute to the symptoms of hemorrhoids by interrupting blood flow and increasing blood stasis and tissue congestion.

15 Varicose veins are enlarged, twisted superficial veins. Varicose veins partially result from incompetent venous valves that may be acquired or congenital.

Venous insufficiency results from
20 increase tone (partial constriction) of the deeper veins (particularly in muscles) which impedes good circulation and results in blood pooling and stasis. This is turn results in pain, tenderness and edema. The problem appears
25 to be related to inadequate draining of the leg veins due to constriction of the exit vein valves. 5-hydroxytryptamine (5-HT or serotonin) is released from the blood platelets when the blood sits around for a long time and is thought
30 to mediate the contraction of the exit veins.

In wounds, 5-HT is released from blood platelets causing venous constriction and interfering with good drainage and circulation. Good drainage and circulation are needed for
35 proper and fast healing of the wounds.

This invention is directed to compositions or medicines useful in treating or

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preventing such conditions as hemorrhoids, varicose veins, venous insufficiency and wounds. In particular it comprises use of a 5-hydroxytryptamine-2 receptor antagonist (5-HT₂) to treat an animal or human, in need of such treatment. The 5-HT₂ receptor antagonist can also be used prophylactically. The 5-HT₂ receptor antagonist is used at an effective therapeutic dose. Preferred 5-HT₂ receptor antagonists include 2'-[2-(1-methyl-2-piperidyl)ethyl] cinnamanilide hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride and any mixture thereof. The 5-HT₂ receptor antagonist 2'-[2-(1-methyl-2-piperidyl)ethyl] cinnamanilide hydrochloride is disclosed and claimed in U.S. Patent Re. 30, 811 (Dysktra et al. Mead Johnson & Company). The 5-HT₂ receptor antagonist 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride is disclosed in U.S. Patents 4,338,317 and 4,487,773. The 5-HT₂ receptor antagonist 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro [4,5] decane-7,9-dione hydrochloride is disclosed in German Patent DE 3,247,530 and U.S. Patent 4,411,901.

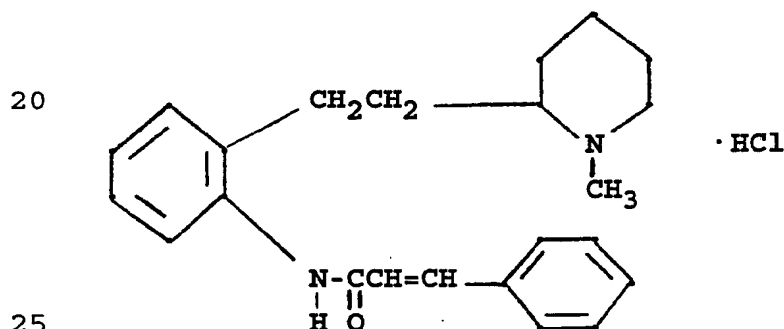
In a series of experiments using rings of human colon veins representative 5-HT₂ receptor antagonists were found to produce highly surprising results in blocking the contractile effects of 5-HT on the human colon. Human colonic vein rings were isolated from discarded human colon tissue following surgery (colostomy). The rings were prepared

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immediately after surgery and were suspended in buffered physiological saline. The contractions produced by the rings in response to the addition of 5-HT in vitro were measured. The effects of three selected 5-HT₂ receptor antagonist compounds on antagonizing 5-HT contractile effects were also determined.

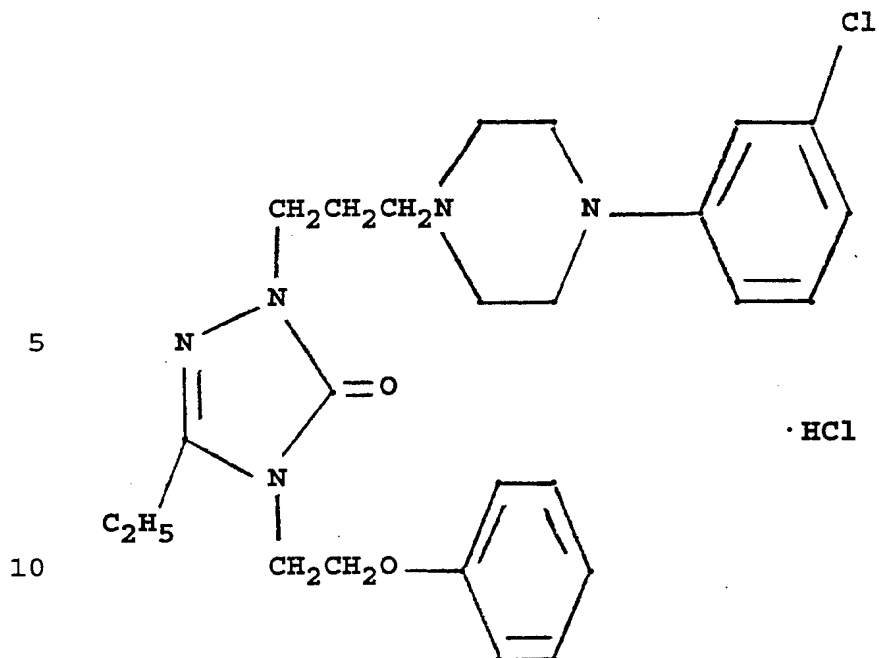
The following tables list the three compounds used and the activity of each in blocking the contractile effects of 5-HT on the human colon in vitro. Table A also includes the activities of the three compounds on four receptors to determine receptor selectivity.

Compound I as used herein has the chemical formula: 2' [2-(1-methyl-2-piperidyl)ethyl] cinnamanilide hydrochloride, and has the following structural formula:

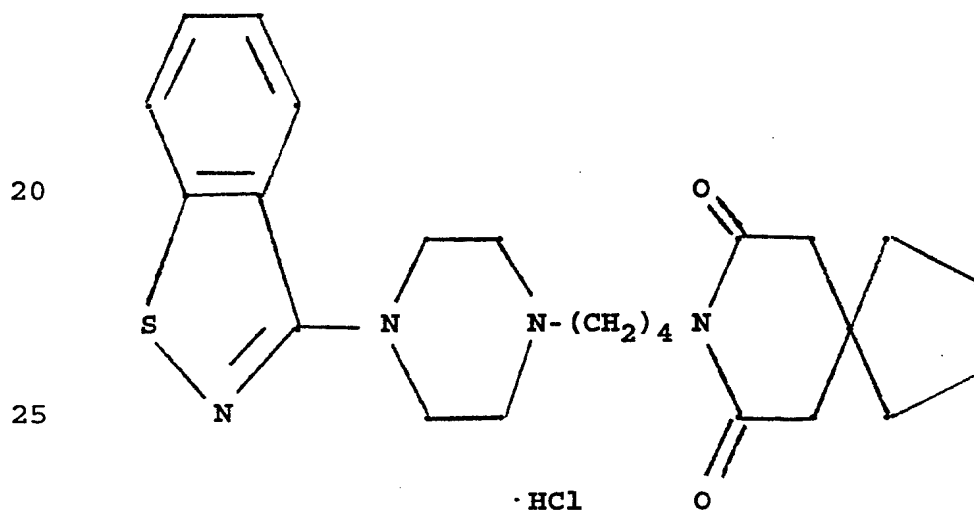


Compound II as used herein has the chemical formula: 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, and has the following structural formula:

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Compound III as used herein has the chemical
 formula: 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-
 15 piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-
 dione hydrochloride, and has the following
 structural formula:



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Table A

Receptor Blocking Profile (IC₅₀ - 50;nm) [nM == nanomolar or 1x 10⁻⁹M]

	Receptor	Compound I	Compound II	Compound III
5	5-HT ₂	3.4	17.0	1.7
	5-HT ₁	22,000.0	>1,000.0	12.5
	Dopamine-2	>1000.0	>1000.0	8.4
	Alpha-receptor	>1000.0	160.0	47.0

The IC-50 is the concentration that
 10 inhibits agonist binding to the receptor by 50%.
 The better the blocker a compound is, the
 smaller is the concentration thereof needed to
 block the receptor, i.e., the smaller the IC-50,
 the better receptor blocker or antagonist the
 15 compound is.

The activity is determined as follows:
 Rings of human colon veins are prepared and hung
 in a tissue bath. The contractions of the rings
 are monitored. Adding 5-HT causes the rings to
 20 contract. Pre-addition of increasing
 concentrations of the antagonist result in
 lesser contractions. The amount of antagonist
 causing a 50% inhibition of the contractions is
 then calculated.

The receptor blocking profile is
 25 determined as follows: Labeled 5-HT is mixed
 with a purified preparation containing the
 receptor. The amount of labeled material that
 attaches itself to the receptor and cannot be
 30 washed off is calculated. In a series of other
 similar tubes, the same quantity of labeled 5-HT
 is mixed with increasing concentrations of the
 antagonist which will antagonize the binding of
 5-HT to the receptor. Decreasing quantities of
 35 the labeled material will bind to the receptor.
 The concentration of the antagonist that
 inhibits the binding of 50% is then calculated.

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Table BActivity against 5-HT on the human colon in vitroIC-50 2×10^{-9} (I) 10^{-8} (II) 10^{-9} (III)

5 As is evident from the above data, although the compounds I, II, and III possess widely different activities against the different receptors tested, their activities in blocking the contractile effects of 5-HT on
10 human colon rings correlated best with their 5-HT₂ blocking potencies.

 Since these three compounds differ significantly from each other chemically, one can conclude that their antagonism of the
15 effects of 5-HT on the human colon is due primarily to their function in blocking the 5-HT₂ receptors in that tissue. Thus, other 5-HT₂ receptor antagonists, irrespective of their chemical structure or other properties, should
20 antagonize 5-HT and block its contractile effects on the human colon.

 An experiment was performed and established that 2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride (MPEC) does
25 not lower blood pressure. This is a classical pharmacological experiment designed to test the effects of new drugs on blood pressure:

 Beagle hounds of either sex weighing 8 - 20 kg were acclimated (18 - 29°C, humidity 30
30 - 70%) for a minimum of 21 days with automatically controlled illumination (12 hours light/12 hours dark) prior to use. Each animal received approximately 300 grams of Purina Lab Canine Diet #5006 daily
35 which was adjusted as needed for each animal to maintain appropriate body weight. Husbandry practices and veterinary care

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were in accordance with the Guide for Care and Use of Laboratory Animals (NIH Publication No. 85 - 23)

5 Animals were fasted on the morning of the experiment and anesthetized with pentobarbital sodium 35 mg/kg i.v. Each animal was intubated with cuffed endotracheal tube to maintain respiration with Bird Mark 7 respirator. Arterial
10 blood pressure (right femoral artery) was measured with Statham P23Db or P23Gb pressure transducer (Gould Statham Instruments, Halo Rey, PR). Heart rate was calculated from the pressure recordings.
15 Other parameters were also monitored. The right femoral vein was cannulated for administration of supplemental anesthesia, and the left femoral vein for administration of vehicle or test drug.
20 When give intravenously, MPEC in a dose of 1 mg/kg elicited no effect on blood pressure or heart rate. A dose of 10 mg/kg was lethal in both dogs tested.

 The effects of MPEC on patients with
25 hemorrhoids was studied. This was a double-blind study. The drug was applied as a 1% cream three times a day. Patients maintained a symptom diary each day. The diary included evaluation of each symptom on a 10 point scale.
30 The results described represent the improvements in the scale between days 1 and 5. The results are depicted in the accompanying graph. The actual numbers of score improvements were as follows:

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	<u>Parameter</u>	<u>Placebo</u>	<u>MPEC</u>	<u>% Improvement</u>
	Pain	0.71	2.14	301.4
	Itching	1.42	2.00	140.8
	Bleeding	-0.43	1.43	>1000.0
5	Tenderness	0.86	2.71	315.1
	Fullness	0.80	4.50	562.5
	Throbbing	0.80	1.75	218.8

The results also support the conclusion that MPEC is working in hemorrhoids via 5-HT₂ receptor blockade since the main effect appears to be on fullness and bleeding. It is expected that a product blocking 5-HT₂ receptors in the colon veins will help with the drainage and will reduce the feeling of fullness that patients with hemorrhoids feel. Since there will be less blood trapped in the swollen veins, less bleeding is also expected. None of the medications presently available on the market have an effect on these two parameters.

The 5-HT₂ receptor antagonists of this invention may be used topically or systemically, and they may be taken orally, in liquid, powder, table or capsule form; parenterally, by intravenous, subcutaneous, or intramuscular injection; transdermally, topically by direct application in the form of a cream, gel, or ointment; rectally by suppository or enema; or by inhalation therapy. The 5-HT₂ receptor antagonists of this invention may be prepared and used in any suitable solid or liquid form, e.g. powder, cream, paste, table, lozenge, gel, chewing gum, solution, suspension, emulsion, salve, aerosol or the like. They may also be incorporated into wound dressings such as bandages, adhesive strips, and other forms designed to be used for wounds. These pharmacological agents may be administered in

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admixture with a pharmaceutically acceptable carrier or a dermatologically acceptable carrier for the topical preparations.

The compositions contain the active
5 ingredient in an amount ranging from less than 1% to over 99%, with the remainder being a pharmaceutically acceptable or dermatologically acceptable solid or liquid carrier, which may contain other conventional excipients. Example
10 of such carriers and excipients include fillers, binders, flavors, sweeteners, bulking and coloring agents, antioxidants, anionic, nonionic, cationic, zwitterionic, and amphoteric surface active detergents, sudsing, dispersing
15 and emulsifying agents, buffering and pH adjusting agents, water and organic solvents, humectants, thickeners, preservatives, stabilizers, mold release agents, disintegrates, anti-distingebrants, lubricants and the like.
20 Examples of conventional pharmaceutically acceptable carriers and excipients are profusely disclosed in the prior art including discussions in U.S. 4,515,772 (Parran et al. Procter & Gamble), U.S. 4,966,777 (Gaffar et al.,
25 Colgate-Palmolive Company), and U.S. 4,728,512 (Mehta et al. American Home Products), which discussions are incorporated herein by reference thereto.

The topical compositions typically
30 contain from 0.1 to 20 weight % of a 5-HT₂ receptor antagonist. Preferably, they contain from 0.5 to 10 weight %. More preferably, from 1 - 5 weight %.

Transdermal compositions typical
35 contain from 0.1 to 20 weight % of a 5-HT₂ receptor antagonists. Preferably, they contain from 0.5 to 10 weight %. More preferably, from

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1- 5 weight %.

Suppositories typically contain from 0.1 to 20 weight % of a 5-HT₂ receptor antagonist. Preferably, they contain from 0.5 to 10 weight %. More preferably, from 1- 5 weight %.

Wound dressings typically contain from 0.1 to 20 weight % of a 5-HT₂ receptor antagonist. Preferably, they contain from 0.5 to 10 weight %. More preferably, from 1- 5 weight %.

Suitably the compositions of this invention consist of sufficient material to provide a dose of from 0.05 - 10 mg. per kg. of body weight, more suitably 0.2 - 6 mg/kg body weight. These compositions may be taken 1 - 3 times daily or as needed until the pain or symptoms of the conditions have subsided.

It will be understood that the foregoing discussion including the examples, only illustrates the invention and its principles. However, many modifications and variations in the details of the disclosure will occur to those skilled in the art to which this invention relates and still remain within the scope and principles of the invention. For example, the illustrative embodiments of the invention deal primarily with several specific 5-HT₂ receptor antagonists. It is apparent, however, that the principles of the invention can be applied to other 5-HT₂ receptor antagonists as well.

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C L A I M S

1. Use of a 5-HT₂ receptor antagonist for the manufacture of a medicament for the treatment or prevention of venous conditions.
- 5 2. A medicine for treatment or prevention of venous conditions characterized in that the medicine comprises a therapeutically acceptable amount of a 5-HT₂ receptor antagonist in a carrier.
- 10 3. A method of treating or preventing venous conditions such as hemorrhoids, varicose veins, venous insufficiency or wound healing characterized by administering to an afflicted or susceptible patient a 5-HT₂ receptor
15 antagonist at a therapeutically effective dose.
4. Use of a 2-HT₂ receptor antagonist to treat or prevent hemorrhoids, varicose veins, venous insufficiency or wounds.
5. A medicine, use or treatment according
20 to any one of the preceding claims, wherein the 5-HT₂ receptor antagonist is 2' [2-1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-
25 triazol-3-one hydrochloride; 8-[4-[4-(1,2-benzisotriazol-3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride or any mixture thereof.
6. A medicine, use or treatment according to
30 any one of the preceding claims, wherein the venous conditions are hemorrhoids, varicose veins, venous insufficiency or wound healing.
7. A topical composition characterized by a 5-HT₂ receptor antagonist in a
35 dermatologically acceptable carrier.
8. A topical composition according to Claim 7, wherein the 5-HT₂ receptor antagonist

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is 2' [2-(1-methyl-2-piperidyl) ethyl]
cinnamanilide hydrochloride; 2-[3-[4-(3-
chlorophenyl)-1-piperazinyl] propyl-5-ethyl-2,4-
dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-
one hydrochloride; 8-[4-[4-(1,2-benzisotriazol-
3-yl)-1-piperazinyl]butyl]-8-azaspiro[4,5]
decane-7,9-dione hydrochloride or any mixture
thereof.

9. A topical composition according to
Claims 7 or 8, wherein the amount of the 5-HT₂
receptor antagonist is from 0.1 to 20 wt %.
10. A topical composition according to
Claims 7-9, wherein the amount of the 5-HT₂
receptor antagonist is from 0.5 to 10 wt %.
11. A suppository characterized by a 5-HT₂
receptor antagonist in a pharmaceutically
acceptable carrier.
12. A suppository according to Claim 11,
wherein the 5-HT₂ receptor antagonist is 2' [2-
(1-methyl-2-piperidyl) ethyl] cinnamanilide
hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-
piperazinyl] propyl-5-ethyl-2,4-dihydro-4-(2-
phenoxyethyl)-3H-1,2,4-triazol-3-one
hydrochloride; 8-[4-[4-(1,2-benzisotriazol-3-
yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-
7,9-dione hydrochloride or any mixture thereof.
13. A suppository according to Claims 11-
12, wherein the amount of the 5-HT₂ receptor
antagonist is from 0.1 to 20 wt. %.
14. A suppository according to Claims 11-
13, wherein the amount of the 5-HT₂ receptor
antagonist is from 0.5 to 10 wt %.
15. A wound dressing characterized by a 5-
HT₂ receptor antagonist in an acceptable
carrier.
16. A wound dressing according to claim
15, wherein the 5-HT₂ receptor antagonist is

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2' [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide
hydrochloride; 2-[3-[4-(3-chlorophenyl)-1-
piperazinyl] propyl-5-ethyl-2,4-dihydro-4-(2-
phenoxyethyl)-3H-1,2,4-triazol-3-one

5 hydrochloride; 8-[4-[4-(1,2-benzisotriazol-3-
yl)-1-piperazinyl]butyl]-8-azaspiro[4,5] decane-
7,9-dione hydrochloride or any mixture thereof.

17. A wound dressing according to claims
15 or 16, wherein the amount of the 5-HT₂

10 receptor antagonist is 0.1 to 20 wt.%.

18. A wound dressing according to claims
15-17, wherein the amount of the 5-HT₂ receptor
antagonist is from 0.5 to 10 wt.%.

FIG. 1

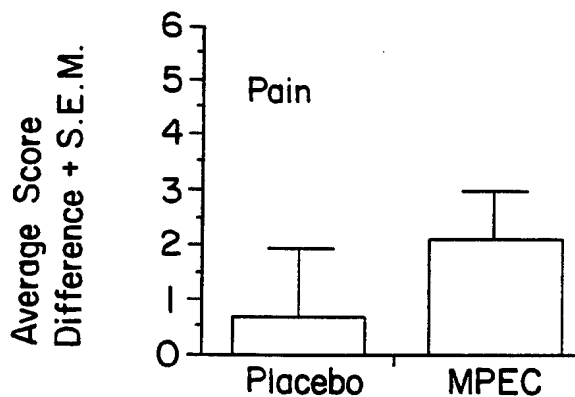


FIG. 2

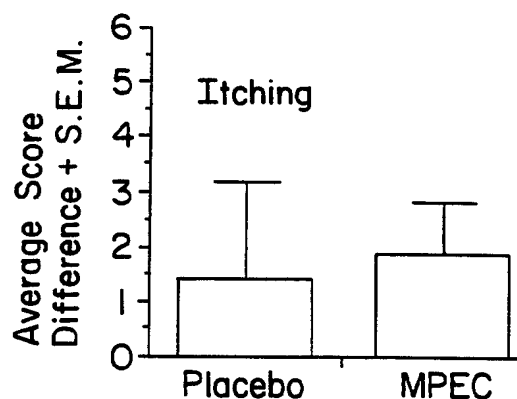


FIG. 3

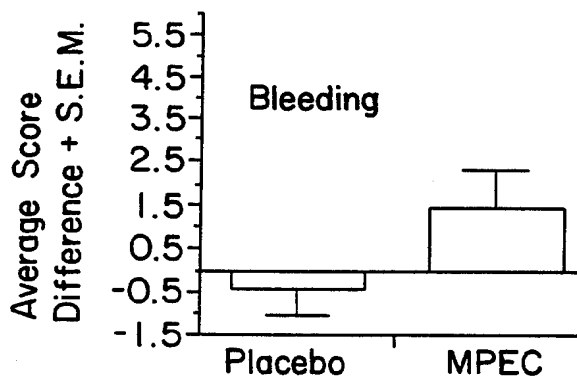


FIG. 4

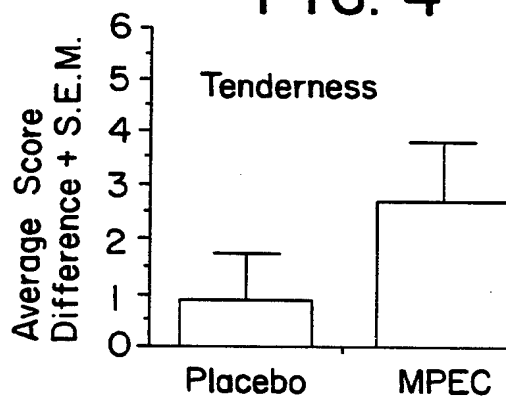


FIG. 5

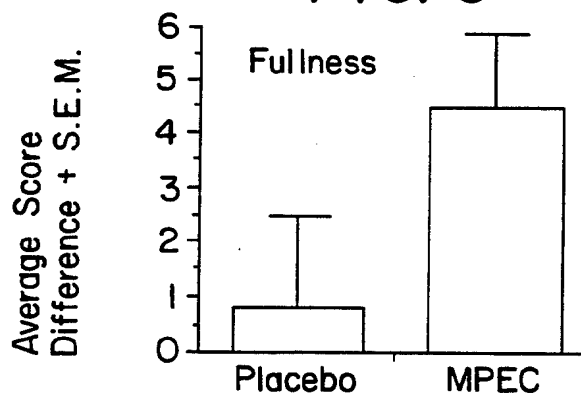
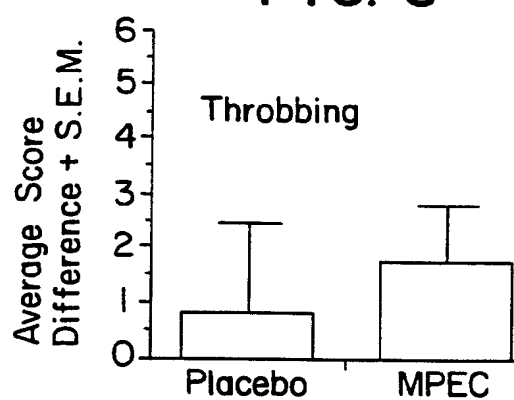


FIG. 6



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/01485

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 A61K31/00; A61K31/445; A61K31/495		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	US,A,4 064 254 (DYKSTRA ET AL.) 20 December 1977 * see column 2 lignes 35 - 55 ; claims 11-20 *	2,5,6
X	US,A,4 411 901 (TEMPLE JR) 25 October 1983 * column 12 lines 22-55; claims 1-9, 12 *	2,5-8
X	US,A,4 487 773 (TEMPLE JR.) 11 December 1984 * see colonne 8 lines 41-68; the claims *	2,5-8
Y	* column 4 lines 30 -31 *	1,3,4, 9-10, 15-18
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
27 SEPTEMBER 1993	12. 10. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	B. ISERT	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	DERMATOLOGICA vol. 178, 1989, pages 98 - 102 ROELENS P., 'Double- blind placebo-controlled study with topical 2% ketanserine ointment in the treatment of venous ulcers' * see the whole document *	1-4,6,7, 9-10,15, 17,18
Y	* p. 98 "Introduction *	1,3,4,9, 10,15-18
X	EP,A,0 526 434 (BOEHRINGER INGELHEIM ITALIA) 3 February 1993 * see page 10 lines 12-16, and page 13 lines 35-42	2,6,7,11
X	PROG. CLIN. BIOL. RES. vol. 365, 1991, pages 115 - 128 ROOMAN RP. ET AL. 'Ketanserine promotes wound healing: clinical and preclinical results' * see the whole document *	1-4,6,7, 9,10,15, 17,18
Y	* see pages 115-118, 124 -125 (discussion) *	1,3,4,9, 10,15-18

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9301485
SA 71521

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